L22: Entry 1 of 6 File: USPT Jul 23, 2002

DOCUMENT-IDENTIFIER: US 6423318 B1
TITLE: Hepatitis A virus vaccines

Brief Summary Text (6):
Research in HAV vaccines has focused on inactivated, or killed, viruses. However, in vaccine therapy there are several advantages to a live vaccine, rather than an inactivated, vaccine. With a live vaccine, one can use a lower dosage and smaller number of doses, because a live vaccine replicates in the vaccinee to produce more antigen and can stimulate the immune system of the vaccinee to make both IgA and IgM. Inactivated vaccines, such as the Salk polio vaccine which stimulates production of IgG only in vaccinees, do not protect against infection by ingested virus, only against disease.

Brief Summary Text (8):
U.S. Pat. Nos. 4,532,215 and 4,636,469 describe, respectively, a strain of wild-type HAV, designated HM-175 [see FIG. 6 below; also SEQ ID NOS: 1 and 2], initially isolated from human feces of a patient in Melbourne, Australia, and adapted to passage in vitro in African green monkey kidney (AGMK) culture cells and methods for obtaining same by serial passaging. U.S. Pat. No. 4,620,978 describes a vaccine employing the HAV HM-175, triply cloned in AGMK cell culture and attenuated. U.S. Pat. No. 4,894,228 describes the HAV strain, HM-175, Pass 35, passaged 35 times in AGMK, which differs from wild-type HM-175 by nucleotide changes in the genome, is attenuated for chimpanzees, elicits serum neutralizing antibodies, and is suitable for use as an attenuated HAV vaccine. It discloses the complete nucleotide sequence of clone 7 of the HAV, designated HM-175/7 or pHAV/7. See FIG. 6 below; the nucleotide changes in pHAV/7 from wt HM-175 appear above the wt sequence; the amino acid changes in pHAV/7 from wt HM-175 appear below the wt amino acid. See, also, B. C. Ross et al, J. Gen. Virol., 70:2805-2810 (1989); R. W. Jansen et al, Virol., 163:299-307 (1988); and Tedeschi et al, J. Med. Virol., 39:16-22 (1993). The disclosures of these patents and articles are incorporated by reference herein.

Brief Summary Text (9):
N. Fineschi et al, J. Hepatol., 13(4):S146-S151 (1991) describes an HAV isolate, LSH/S, which is a candidate for an inactivated vaccine. It was adapted to grow in human diploid MRC-5 cells, a preferred licensed cell for vaccine development. This document compares only a small part of its nucleotide sequence to that of wild-type HM-175.

Brief Summary Text (12):
A live attenuated hepatitis A vaccine could have a significant impact on the eradication of the disease. It could be anticipated that a live attenuated vaccine which requires minimal purification and no adjuvant would be less costly than presently available inactivated hepatitis A vaccines.

Detailed Description Text (2):
The present invention provides hepatitis A virus (HAV) adapted to growth in the human fibroblast-like cell line, MRC-5, a cell substrate suitable for commercial production and licensing of inactivated and live, attenuated hepatitis A vaccines. In addition to such adapted HAVs, the invention provides a method for adapting a selected HAV to growth in that human cell line and preparing an MRC-5-adapted, attenuated HAV without passaging in other primate cells. The HAV of this invention and the preparative method also preferably provides the HAV with sufficient attenuation to enable its efficacy as

a vaccine for humans and animals.

Detailed Description Text (12):
A candidate inactivated hepatitis A vaccine was prepared from the HAV 4380 and demonstrated to be safe (i.e., it does not produce hepatitis or other serious adverse effects) and immunogenic in humans. It was also found to induce antibody production without adjuvant. HAV 4380, as it currently exists, grows well in a cell substrate suitable for commercial vaccine production. It also does not infect human beings when administered by the oral or intravenous route at doses of up to 10.sup.7 tissue culture infectious doses, even when not inactivated. HAV 4380 is suitable for use as a live HAV vaccine in humans. However, as indicated in Example 2, vaccine 4380 is believed to be somewhat over-attenuated, because it is not infectious, which characteristic reduces its efficiency when used as an attenuated vaccine.

Detailed Description Text (14):
Thus, knowledge of the genomic differences between the AGMK-adapted passages of HM-175 and the more attenuated 4380 permit the construction of chimeric viruses having the improved growth characteristics, i.e., rapid and efficient growth in MRC-5 cell culture, but with a level of attenuation of virulence for primate species, including man, that will permit the virus to replicate efficiently without producing hepatitis or other untoward effects. This invention permits the design of a chimeric HAV that can achieve the optimum characteristics for a candidate live-attenuated hepatitis A vaccine. Such a virus will also permit the design of preferred inactivated vaccine candidates, if desired. The present invention identifies the mutations that are believed to have occurred during adaptation to growth of the HM-175 HAV, passage 32, strain in MRC-5 cells. One or a combination of these mutations are responsible for MRC-5 cell adaptation and overattenuation in HAV 4380.

US Reference Patent Number (3):
4636469

US Reference Group (3):
4636469 19870100 Daemer et al.

Other Reference Publication (15):
F. Andre et al., "Inactivated Candidate Vaccines for Hepatitis A", Prog. Med. Virol. Base. Karger, 37:72-95 (1990).

Other Reference Publication (28):
F. Andre, "Approaches to a Vaccine Against Hepatitis A: Development and Manufacture of an Inactivated Vaccine", J. Infect. Dis., 171 (Suppl 1):S33-S39 (Mar., 1995).

Other Reference Publication (29):
J. Peetermans, "Production, Quality Control and Characterization of an Inactivated Hepatitis A Vaccine", Vaccine, 10(Suppl 1):S99-S101 (Nov., 1992).

Other Reference Publication (30):
F. Andre, "Hepatitis A in Travellers: Development of a Safe, Immunogenic and Efficacious Inactivated Vaccine", Travel Medicine International, 13(1):10-14 (Jan., 1995).

Other Reference Publication (31):
Product Insert, "HA:L3A Prescribing Information, Hepatitis A Vaccine, Inactivated Havrix", Distributed by SmithKline Beecham Pharmaceuticals (Feb., 1995).